Remarks

Claims 1, 3, and 6-7 are pending after entry of the amendments set forth herein. Claims 2, 4-5, and 8-14 are canceled without prejudice. Claims 1, 3 and 6 have been amended for clarification. Support for these amendments is found in throughout the original claims and specification, including, for example, p. 5, lines 1-18; and p. 24, lines 8-end of page. Therefore, no new matter is added. Reconsideration is requested.

OBJECTIONS TO THE CLAIMS

Claims 1 and 3 are objected to because the claim includes subject matter of the non-elected inventions, namely the detection of a mutation in a protein (Groups III and IV), and with respect to claim 1, the detection of the mutations other than K8R340X.

Claims 1 and 3 have been amended to recite that the mutation detected is in a codon encoding K18 or K8, and therefore these claims as amended are directed to elected Group I, which includes analyzing nucleic acids. With respect to detection of mutations other than K8 R340X as in Claim 1, the Applicants maintain that as the Office has stated that claim 1 has only been examined to the extent that the claim reads on the elected invention of detecting a predisposition to liver disease by assaying for a nucleic acid mutation resulting in the K8 R340X alteration (Final Office Action, p. 2), this claim has not been further limited in view of the previous species election, as the claim shall be restricted to this species if no generic claim is finally held to be allowable.

Therefore, in view of the amendments, withdrawal of the objections is requested.

REJECTIONS UNDER §112, ¶2

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office has stated that the claims do not recite a clear nexus between the preamble of the claims and the final process step of the claims, and that the claims further omit the essential step of actually detecting a predisposition to a liver disease (Final Office Action, p. 3-4).

Independent claims 1 and 3 have therefore been amended to recite a step of "determining said predisposition to noncryptogenic liver disease". This amendment adds the

step of detecting a predisposition to a liver disease, and also clarifies that the method of determining a predisposition to noncryptogenic liver disease in the preamble is clearly linked to the final process step in the body of the claim, and therefore this rejection may be withdrawn.

Claim 1 has also been amended to add the limitation of "noncryptogenic" to the preamble, to clarify that the claims are directed to detection of noncryptogenic liver disease in an individual human and therefore this rejection may be withdrawn.

The Office has also alleged that Claims 6 and 7 are indefinite over the recitation of "said analyzing the genomic or mRNA sequences" because the phrase lacks antecedent basis. Claim 6 has been amended to recite "analyzing the nucleic acid", as recited in Claim 3, and therefore this rejection may be withdrawn.

Claims 1, 3, 6 and 7 have been rejected as indefinite because the preamble recites "an individual human", while the method step in the body of the claim recites analyzing "an individual". The claims have been amended to clarify that the method is a method for detecting a predisposition to noncryptogenic liver disease in an individual human, and therefore this rejection may be withdrawn.

Claim 1 has been rejected as being indefinite for reciting "said alteration" because the phrase lacks antecedent basis. Claim 1 has been amended to recite "said change", and therefore this rejection may be withdrawn.

Claims 3, 6 and 7 have been rejected as indefinite because the claims refer to a step of analyzing for a change in genotype but then recite that a mutation at position 340 is associated with a predisposition to noncryptogenic liver disease, and the claims further do not recite what the change is relative to. Applicants note that the amino acid numbering does not include the first methionine, which is cleaved posttranslationally. Claim 3 has therefore been amended to clarify that the change is a change in codon genotype encoding keratin K8 at position 340, and further that the change is relative to the wild-type sequence, and therefore this rejection may be withdrawn.

In view of the above amendments, withdrawal of the rejections is requested.

REJECTIONS UNDER §112, ¶1

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Office has alleged that the specification, while enabling for methods of identifying a human subject at increased risk for viral hepatitis or acute fulminant hepatitis, does not reasonably provide enablement for the scope of the claims.

Without conceding to the correctness of the rejection, Applicants have amended Claim 3 to recite the subject matter stated to be enabled by the Examiner. Withdrawal of the rejection with respect to Claim 3 is requested in view of the amendment.

Applicants respectfully submit that Claim 1 meets the requirements of 35 U.S.C. 112, first paragraph.

Applicants have previously submitted data from the present inventors regarding the importance of keratin 8 variants in acute liver failure and the importance of some K8 variants in African Americans with liver disease and in African American in general. Applicants note that the data previously provided has been submitted to the New England Journal of Medicine (additional copy attached).

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

The instant specification teaches multiple mutations, both in keratin K8 and in K18, that are associated with liver disease, as shown in Tables 3 and 4, which mutations cover a number of different residues in these proteins. It is noted that many of these mutations have an underlying molecular logic, in that there is a destabilization of the protein, providing for a logical nexus between genetic defect and disease. As cited in Ku, et al. (*Keratin Mutations Predispose*

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1 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2 *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

to Cryptogenic and and Noncryptogenic Liver Disease; Gastroenterology, 2002, cited in IDS), there is an "extensive body of transgenic animal data showing that keratins play an essential role in protecting hepatocytes from mechanical and nonmechanical stresses". For example, Table 6 shows the molecular consequences of keratin mutations:

Table 6. Molecular Consequences of Keratin mutations

Mutations		Potential effects
K8	R340H	Destabilization
	G433S	Altering keratin phosphorylation
	R453C	Formation of a disulfide bond
	1-465(I) RDT(468)	Destabilization
K18	Δ 64-71(TGIAGGLA)	Destabilization
	E275G	Destabilization
	Q284R	Destabilization
	T294M	Interruption of ionic interaction
	T296I	Interruption of ionic interaction

The significant number of patients described in the present application with K8/K18 mutations provide several insights into keratin-associated liver diseases. For example, K8 Y53H, K8 G61C, and most prominently K8 R340H are shown to be mutation hot spots.

Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

"[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular

3 See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art, which routinely performs such long experiments.[5]

The claimed methods relate to the use of the many different polymorphisms for keratin K8 and K18 that are provided in the application. The sequence of polynucleotides is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on different samples. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay to determine the active variants, no undue experimentation is necessary.

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7] As discussed above, numerous working examples have been provided.

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with the equivalent of a doctoral degree in molecular biology techniques, although Applicants believe that a much lower skill level would be sufficient to perform the claimed methods. Furthermore, such technicians are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

There may be some non-functional variants within the genus defined by the claims. However, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

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4 *In re Wands* 8 USPQ 2d at 1404
5 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)
6 In re Borkowski, 164 USPQ at 645.
7 *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

The court has very clearly explained[8]:

"To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

In sum, the amount of experimentation required to practice the methods of the invention would not be undue because a) a working example has been provided, b) guidance is given on how to test the sequences has been provided, and c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the sequences.

The Office Action has stated that "it is well-recognized in the art that associations between polymorphisms and phenotypic traits are often irreproducible". Applicants submit that the present invention is based not only on association studies, but on supporting animal models. Further, the use of association studies is well-supported in guiding human health decisions. For example, the odds ratio for liver failure associated with the genetic markers of the present invention is higher than the odds ratio for the well-known association of smoking and heart disease.

Applicants submit that the recent Board decision, Appeal 2009-0938, Ex parte Walsh et al. (copy attached) is relevant to the facts of the present application.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. In view of the above amendments and remarks, withdrawal of the rejection is requested. Applicants note that Claim 3 as presently amended is restricted to determination of a change in codon genotype at position 340 of keratin K8 from CGT→CAT relative to wild-type sequence, for a detecting a human subject at increased risk for noncryptogenic liver disease.

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8 *In re Angstadt*, 190 USPQ at 218.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-297.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 29, 2009

By: _____
Pamela J. Sherwood, Ph.D.
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231